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Yasuko Ozaki

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FOLEY AND LARDNER LLP  
SUITE 500  
3000 K STREET NW  
WASHINGTON, DC 20007

EXAMINER

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 09/622,646	<b>Applicant(s)</b> OZAKI ET AL.	
	<b>Examiner</b> Christine Foster	<b>Art Unit</b> 1641	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 28 March 2011.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-4 and 6-19 is/are pending in the application.
- 4a) Of the above claim(s) 3, 4, 10-12 and 14-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,6-9,13 and 17-19 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 August 2000 and 19 September 2008 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>3/28/2011</u> .   | 6) <input type="checkbox"/> Other: _____                          |

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## **DETAILED ACTION**

### **Amendment Entry**

1. Applicant's amendment, filed 3/28/2011, is acknowledged and has been entered. Claims 1 and 17-18 were amended. New claim 19 has been added. Accordingly, claims 1-2, 6-9, 13, and 17-19 are subject to examination below in light of the elected species of a protein having the amino acid sequence modified by lacking 17 amino acid residues from the C-terminal of SEQ ID NO:20.

### **Objections/ Rejections Withdrawn**

2. The objection to claim 18 is withdrawn in response to Applicant's amendments.

### **Priority**

3. The present application was filed on 8/21/00 and is a national stage (371) entry of PCT/JP99/00885, filed 2/25/99. Acknowledgment is also made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Application No. 10-60613, filed on 2/25/98 in Japan.

### **Information Disclosure Statement**

4. Applicant's Information Disclosure Statement filed 3/28/2011 has been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449/ PTO/SB/08a.

Citations F2 and F4 have been lined through to avoid duplicate citation on the face of any issuing patent, as the references are already of record.

### **Claim Rejections - 35 USC § 103**

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-2, 6-7, 13, and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane (Harlow, E. and Lane, D., Antibodies: A Laboratory Manual (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pages 7, 555, 560-577, and 591-592) in view of Ishikawa et al. ("Molecular cloning and chromosomal mapping of a bone marrow stromal cell surface gene, BST2, that may be involved in pre-B-cell growth" Genomics. 1995 Apr 10;26(3):527-34), Gastinel et al. (U.S. 5,623,053), Lauffer et al. (U.S. 5,639,597), Laping et al. (U.S. 5,866,693), Lo et al. (U.S. 5,541,087), Matsuzawa et al. (U.S. 5,374,533), and Browning et al. (WO 96/22788).

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Harlow & Lane teach that antibodies are host proteins produced primarily by plasma cells, and circulate throughout the blood and lymph where they bind to antigens (page 7).

To detect antibodies, Harlow & Lane teach antibody-capture assays, in which an antigen is bound to a solid phase in order to capture specific antibody present within a test sample (see page 555, Figure 14.1 in particular; and pages 560 and 562-577).

Such assays are useful, for example, in quantitating antibodies and can be used to compare the epitopes recognized by different antibodies (see especially at page 563, first paragraph). In addition, such assays can be used in a hybridoma screen, in order to screen hybridoma tissue culture supernatants (see page 566, bottom; and page 569). This allows for antibodies that bind to the antigen to be identified.

Harlow & Lane therefore teach immunochemical assays of the same format as claimed instantly, in which an antigen is bound to a solid support and used to detect antibodies specific to the antigen in a test sample. However, Harlow & Lane fail to teach soluble HM1.24 antigen protein as the type of antigen, and similarly fail to teach anti-HM1.24 antibodies as the type of antibodies detected.

Ishikawa et al. teach the antigen BST-2, which is a human membrane protein expressed on bone marrow stromal cells (the abstract). It is noted that BST-2 as taught by Ishikawa et al. is the same protein referred to in the instant specification as HM1.24 antigen. This is evident by referring to the predicted amino acid sequence for the 180-residue BST-2 protein in Figure 4 of Ishikawa et al., which is the same sequence disclosed instantly as SEQ ID NO:16 (the full-length human HM1.24 antigen). The authors conducted functional studies which suggested that this

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antigen may be involved in stimulating pre-B-cell growth (abstract; page 528, left column, first paragraph; page 531, right column, first sentence; and page 532, right column, last paragraph).

When taken together with the teachings of Harlow & Lane, therefore, it would have been obvious to one of ordinary skill in the art to pursue immunochemical antibody-capture assays using the novel BST-2/HM1.24 antigen taught by Ishikawa et al. as the type of antigen in order to detect antibodies specific to BST-2/HM1.24 in a test sample according to the methods of Harlow & Lane. One would be motivated to do this in order to quantify such antibodies and/or to compare their epitopes as part of experiments to further study a newly discovered protein of importance in pre-B-cell growth.

However, Ishikawa et al. further teach that the BST-2/HM1.24 protein is a transmembrane protein (the abstract).

Those of skill in the art at the time of the invention recognized certain technical considerations for dealing with antigens that are transmembrane proteins.

For example, Gastinel et al., in discussing the transmembrane FcRn receptor, teach that the hydrophobic nature of the receptor's transmembrane domain precludes the solubilization of the protein in aqueous buffer without the use of surfactants, which are often toxic, difficult to remove, and can reduce the stability of proteins (column 4, lines 43-50). As a result, the usefulness of the membrane-bound receptor is limited by the fact that, like other transmembrane proteins, is not readily soluble in aqueous solutions without surfactants (column 4, line 66 to column 5, line 2). By contrast, Gastinel et al. teach that there are many applications for an Fc receptor that is soluble in aqueous solutions without the use of a surfactant (column 4, lines 51-65; column 11, lines 62-67). Gastinel et al. further teach that such soluble receptors can be

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produced by removal of the transmembrane domain (column 5, lines 3-20; column 6, lines 1-10; column 10, lines 48-57). In addition, the soluble receptors of Gastinel et al. maintained the ability to bind to antibodies and can be attached to any compatible, functional surface (column 10, lines 42-47; column 11, lines 62-67).

Lauffer et al. discuss how binding experiments involving transmembrane receptor proteins can be carried out while the receptors remain bound to the cell, but that such assays are increasingly difficult as the number of receptors in the cell membrane decreases (column 1, lines 8-35). To avoid this drawback, Lauffer et al. propose receptor binding assays using soluble fusion proteins in place of membrane-bound receptors, in which the extracellular domains of human membrane proteins are fused to the constant part (Fc) of the heavy chain of an Ig (column 1, line 35 to column 2, line 40). Such fusion proteins retain their biological activity (column 1, lines 62-67). The fusion proteins can be produced as secreted proteins in animal cells and easily purified by affinity chromatography via their Fc part, e.g. on a sepharose matrix (column 2, lines 4-18).

Similarly, Laping et al. teach Fc fusion proteins in which proteins or parts thereof are fused to the immunoglobulin constant or Fc region (column 9, line 55 to column 10, line 27). Laping et al. also contemplate fusion proteins involving membrane-bound receptors, in which one or more of the extracellular domain, the transmembrane domain, or the cytoplasmic domains of the receptors are used as components of the fusion protein (column 10, line 28-36).

Laping et al. further teach that for some uses, it is desirable to be able to delete the Fc part after the fusion protein has been expressed and purified (ibid; as well as the abstract and claims 9-12). This is the case when the Fc portion proves to be a hindrance, for example, when

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the fusion protein is to be used as an antigen. This is done by linking the two components of the fusion protein with a cleavable linking region, e.g. a cleavage sequence that can be cleaved with factor Xa.

Lo et al. also teach fusion protein expression systems that enhance the production of a given target protein, in which an encoded target protein is fused to a secretion cassette such as an Fc domain, which allows for purification by binding to protein A. See column 1, lines 5-20; column 2, line 62 to column 2, line 56; and column 4, lines 46-60.

Lo et al. also contemplate production of essentially any target protein using this system, including target proteins that are normally non-secreted proteins. For example, if a desired target protein includes sequences encoding a secretion signal or a transmembrane signal, these sequences can be removed so that the fusion protein is secreted as a soluble protein (column 8, lines 1-21; column 1, lines 16-20). Thus, by using this Fc fusion system, a higher level of protein expression may be obtained (see also column 13, lines 50-55).

Lo et al. further teach that a proteolytic cleavage site is interposed between the encoded target protein and the Fc region, allowing it to be subsequently cleaved (ibid and column 5, lines 8-24; column 3, line 66 to column 4, line 2).

Matsuzawa et al. recognized that nonspecific interactions can occur between Fc sequences and components in a sample such as rheumatoid factor, which results in nonspecific interactions in immunoassays. See column 2, lines 9-32. To avoid this problem of nonspecific interactions, the authors removed the Fc sequence from their immunoassay reagent (in this case, an antibody). See also column 4, lines 41-55.

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Finally, Browning et al. also teach methods of preparing soluble forms of a transmembrane receptor protein, in which the amino acid sequences that localize the protein have been deleted or inactivated; such soluble forms can be secreted by an appropriate host cell (see page 12, lines 3-10). Browning et al. further teach that such soluble receptors can be prepared as either a soluble extracellular domain, or as chimeric proteins with the extracellular ligand binding domain coupled to an immunoglobulin Fc domain. See page 18, lines 13-18.

The teachings of Gastinel et al., Lauffer et al., Laping et al., Lo et al., and Browning et al. indicate that those of skill in the art recognized certain technical obstacles that may arise when working with transmembrane proteins. In addition, these references indicate that in order avoid such obstacles, it was known to use soluble forms of such transmembrane proteins (for example, proteins lacking the transmembrane region and/or soluble receptor-Fc fusion proteins) in place of the full-length, membrane-bound proteins.

In this regard, it is noted that in addition to identifying BST-2/HM1.24 as a transmembrane protein, Ishikawa et al. (discussed above) also constructed a **soluble** form of BST-2/HM1.24, in which the putative extracellular region of was fused to the Fc region of human IgG1 (see page 527, right column, "Production of soluble recombinant BST-2/HM1.24-immunoglobulin fusion protein"; and also at page 530, left column, first paragraph; and Figure 4).

When taken together with the teachings of Gastinel et al., Lauffer et al., Laping et al., and Lo et al. and Browning et al., it would have been obvious to one of ordinary skill in the art to employ a soluble form of the BST-2/HM1.24 antigen when performing antibody-capture assays for anti-HM1.24 antibodies according to the method of Harlow & Lane and Ishikawa et al. More

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particularly, it would have been obvious to employ BST-2/HM1.24 antigen in which the transmembrane domain had been removed. One would be motivated to use a soluble form instead of the full-length antigen because to avoid potential technical problems known to arise when using full-length transmembrane receptors. For example, it would have been obvious to remove the transmembrane domain and express the extracellular domain of the BST-2/HM1.24 antigen as a fusion protein with Fc as done by Ishikawa et al., in order to enhance production of the antigen using this known Fc fusion protein system (as also taught by Lauffer et al., Laping et al., and Lo et al.).

With respect to the limitation that the soluble HM1.24 antigen protein used in the method is one “consisting the amino acid sequence modified by lacking the last 17 amino acid residues from a C-terminus in the amino acid sequence of SEQ ID NO:20”, Ichikawa et al. illustrate a soluble BST-2/HM1.24 antigen fused to Fc as discussed above. This fusion protein therefore does not consist of the indicated amino acid sequence, since it contains the Fc region in addition to amino acids of BST-2/HM1.24.

However, the prior art as discussed above suggests at least two possible ways at arriving at the claimed invention.

First, in light of the teachings of Gastinel et al. and Browning et al. that soluble forms of a transmembrane receptor may be produced either by deletion of the transmembrane domain or alternatively via construction of an Fc fusion protein, it would have been obvious to one of ordinary skill in the art to prepare the soluble HM1.24 antigen protein by simply removing the transmembrane domain, rather than through use of an Fc fusion as in Ishikawa.

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One would be motivated to prepare soluble HM1.24 in this manner because Matsuzawa et al. taught that it was known in the art that Fc sequences may result in nonspecific binding when used in in vitro immunoassays. Therefore, one would be motivated to remove the Fc sequence from the soluble HM1.24 antigen protein prior to its use in such an immunoassay in order to avoid these known problems.

Alternatively, in light of the teachings of Laping et al., Lo et al., and Matsuzawa et al. as discussed in detail above, it would have been obvious to one of ordinary skill in the art to first produce the soluble BST-2/HM1.24 as an Fc fusion protein and then to subsequently cleave off the Fc region. In particular, these references indicate that it was known in the art to exploit Fc fusion proteins to express and purify soluble proteins, and also that it was known to subsequently remove the Fc tag. As such, it would have been obvious to prepare soluble BST-2/HM1.24 as a fusion protein with Fc (as illustrated by Ishikawa et al.) and then to subsequently cleave off the Fc region, via use of a cleavable linker as taught by Laping et al. and Lo et al.

One would be motivated to do this since as recognized by Laping et al., it can be desirable to delete the Fc part after the fusion protein has been expressed and purified. Additional motivation is provided by Matsuzawa et al. who taught that it was known in the art that Fc sequences may result in nonspecific binding when used in in vitro immunoassays. Therefore, one would be motivated to remove the Fc sequence from the soluble HM1.24 antigen protein prior to its use in such an immunoassay in order to avoid these known problems.

It is also noted that Ishikawa et al. employed a secretory signal sequence from BST-1 in their Fc fusion construct (page 530, left column). However, such sequences were known to be removed by the host cell (Lo et al. column 5, lines 18-32). Even if this did not occur naturally in

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the host cell, Lo et al. teach that such sequences are cleaved (column 2, lines 18-37; see also Figure 1). It is also noted that because the secretory signal sequence is appended at the amino terminus prior to the Fc region, it would also be cleaved off upon removal of the Fc region.

The claim limitation of “a protein consisting the amino acid sequence modified by lacking **the last 17 amino acid residues** from a C-terminus in the amino acid sequence of SEQ ID NO:20” is also interpreted to refer to the amino acid sequence SEQ ID NO:20 in which the last 17 residues of this sequence are absent.

The Examiner notes that the soluble BST-2/HM1.24-immunoglobulin fusion protein taught by Ishikawa et al. corresponds to the portion of HM1.24 from asparagine 49 to serine 162 (see page 527, right column, "Production of soluble recombinant BST-2/HM1.24-immunoglobulin fusion protein"; and also at page 530, left column, first paragraph; and Figure 4). Comparing the sequence information in Figure 4 of Ishikawa et al. with instant SEQ ID NO:20, it can be seen that the sequence Asn 49 to Ser 162 corresponds to the amino acid sequence shown in SEQ ID NO:20, but lacking **the last 18 amino acid residues** of SEQ ID NO:20.

As such, the BST-2/HM1.24 fusion protein of Ishikawa also lacks the last 18, rather than the last 17 residues, of SEQ ID NO:20.

However, the examiner notes that the instant claims require only that the antigen lack 17 the last amino acids. Because the antigen protein of Ishikawa et al. lacks the last 18 amino acids, it also necessarily lacks the last 17 amino acids. As a result in which this manner in which the invention is being claimed, the teaching of an antigen protein lacking the last 18 amino acids (as in Ishikawa et al.) reads on the instantly claimed protein.

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Even presuming that Applicant intends to claim an antigen protein which lacks exactly 17 (and no more) amino acids, the claimed invention is considered obvious for the following reasons.

As noted above, the BST-2/HM1.24 fusion protein of Ishikawa lacks the last 18, rather than precisely the last 17, residues of SEQ ID NO:20.

Figure 4 of Ishikawa:

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                                GTGGGATTC      9
ATG GCA TCT ACT TCG TAT GAC TAT TGC AGA GTG CCC ATG 48
Met Ala Ser Thr Ser Tyr Asp Tyr Cys Arg Val Pro Met 13
GAA GAC GGG GAT AAG CCC TGT AAG CTT CTG CTG GGG ATA 87
Glu Asp Gly Asp Lys Arg Cys Lys Leu Leu Leu Gly Ile 26
GGA ATT CTG GTC CTC CTG ATC ATC ATC GTC ATT CTG GGG GTC 126
Gly Ile Leu Val Leu Leu Ile Ile Val Ile Leu Gly Val 39
CCC TTG ATT ATC TTC ACC ATC AAG GCC AAC AGC GAG GCC 165
Pro Leu Ile Ile Phe Thr Ile Lys Ala Asn Ser Glu Ala 52
TGC CGG GAC GGC CTT GCG GCA GTG ATG GAG TGT CGC AAT 204
Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg Asn 65
GTC ACC CAT CTC CTG CAA CAA GAG CTG ACC GAG GCC CAG 243
Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln 78
AAG GGC TTT CAG GAT GTG GAG GCC CAG GCC GCC ACC TGC 282
Lys Gly Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys 91
AAC CAC ACT GTG ATG GGC CTA ATG GCT TCC CTG GAT GCA 321
Asn His Thr Val Met Ala Leu Met Ala Ser Leu Asp Ala 104
GAG AAG GCC CAA GGA CAA AAG AAA CTG GAG GAG CTT GAG 360
Glu Lys Ala Gln Gly Gln Lys Lys Val Glu Glu Leu Glu 117
GGA GAG ATC ACT ACA TTA AAC CAT AAG CTT CAG GAC GCG 399
Gly Glu Ile Thr Thr Leu Asn His Lys Leu Gln Asp Ala 130
TCT GCA GAG GTG GAG CGA CTG AGA AGA GAA AAC CAG GTC 438
Ser Ala Glu Val Glu Arg Leu Arg Arg Glu Asn Gln Val 143
TTA AGC GTG AGA ATC GCG GAC AAG AAG TAC TAC CCC AGC 477
Leu Ser Val Arg Ile Ala Asp Lys Lys Tyr Tyr Pro Ser 156
TCC CAG GAC TCC AGC TCC GCT GCG GCG CCC CAG CTG CTG 516
Ser Gln Asp Ser Ser Ser Ala Ala Ala Pro Gln Leu Leu 169
ATT GTG CTG CTG GGC CTC AGC GCT CTG CTG CAG TGAGATC 556
Ile Val Leu Leu Gly Leu Ser Ala Leu Leu Gln ... 180
CCAGGAAGCTGGCAGATCTTTGGAAAGGTCCCTCTGCTCGGCTTTTCGCTTG 606
AACATTCCTCCCTGATCTCATCTCTCTGACGGGTCATGGGGCAACAGGCT 657
AGCGGGGAGAGACACCGGGGTAGCCCGAGAGAGGGCCCTCTGGAGCAGGTCTGGA 706
CGCGCCATGGGGCAGTCTCTGGGTGTGGGGACACAGTCCGGGTTGACCCAGGG 759
CTGTCTCCCTCCAGAGCCCTCCCTCCGGACAAATGAGTCGCCCTCTCTGTCTC 810
CCACCCCTGAGATTGGGCATGGGGTCCGGGTGTGGGGGACATGTGCTGCTGT 861
TGTATGGGTTTFTTTTGGGGGGGGGTTGCTTTTCTGCGGGTCTTTGAG 912
CTCCAAAAAATAAACACTTCCTTTGAGGGGAGAGCAAAAAA 963
AAAAAAAAAAAAAAAAAAGATTCCACCACA 996

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FIG. 4. Nucleotide and predicted amino acid sequence of human BST-2 cDNA. The putative transmembrane region is underlined. Two potential sites of N-linked glycosylation are indicated by asterisks. This sequence data have been deposited with DDBJ/EMBL/GenBank under Accession No. D28137.

SEQ ID NO:20 as disclosed instantly:

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<210> 20
<211> 132
<212> PRT
<213> Homo sapiens

<220>
<223> Amino acid sequence of soluble HM 1.24 antigenic
      protein

<400> 20
Asn Ser Glu Ala Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg
 1             5             10             15
Asn Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln Lys Gly
      20             25             30
Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys Asn His Thr Val Met
      35             40             45
Ala Leu Met Ala Ser Leu Asp Ala Glu Lys Ala Gln Gly Gln Lys Lys
      50             55             60
Val Glu Glu Leu Glu Gly Glu Ile Thr Thr Leu Asn His Lys Leu Gln
      65             70             75             80
Asp Ala Ser Ala Glu Val Glu Arg Leu Arg Arg Glu Asn Gln Val Leu
      85             90             95
Ser Val Arg Ile Ala Asp Lys Lys Tyr Tyr Pro Ser Ser Gln Asp Ser
      100            105            110
Ser Ser Ala Ala Ala Pro Gln Leu Leu Ile Val Leu Leu Gly Leu Ser
      115            120            125
Ala Leu Leu Gln
      130

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Therefore, Ishikawa et al. disclose a soluble HM1.24 antigen protein having the amino acid sequence modified by lacking 18 amino acid residues from the C-terminus of SEQ ID NO:20, while the instantly claimed invention recites a protein modified by lacking 17 amino acid residues from the C-terminus of SEQ ID NO:20. In other words, the instant claims invoke proteins comprising the sequence from amino acids 49 to 163 of full-length HM1.24, while the soluble HM1.24 antigen protein of Ishikawa et al. ranges from amino acids 49 to 162. The Ishikawa et al. protein is missing an additional residue from the C-terminus, namely the alanine residue at position 163 of the full-length protein.

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However, the courts have ruled that in the case where the claimed ranges “overlap or lie inside ranges disclosed by the prior art” a prima facie case of obviousness exists. See MPEP 2144.05.

In the instant case, the teachings of Gastinel et al. and Lauffer et al. establish that deleting amino acids from a transmembrane protein was known to have effects on the physical properties of the protein, namely on the protein’s solubility. Lauffer et al. further contemplate soluble fusion proteins composed of “various portions of the extracellular domains of human membrane proteins” (column 1, lines 46-56). Such teachings indicate that the particular amino acids sequence of a transmembrane receptor was known to be a result-effective variable.

Therefore, it would have been obvious to one of ordinary skill in the art to vary the amino acid sequence of the soluble HM1.24 antigen protein of Ichikawa et al. by including an additional amino acid at the region corresponding to the C-terminus of HM1.24. In particular, because Ishikawa et al. taught that the next amino acid in the endogenous sequence of HM1.24 is alanine 163, it would have been obvious to include this residue in the construct. Put another way, it would have been obvious to remove 17 rather than 18 amino acids from the C-terminus of HM1.24 when preparing the soluble HM1.24 antigen protein.

Furthermore, when taken together with the general knowledge in the art that the amino acid alanine is a small amino acid that possesses no reactive groups on its side chain, one would have had a reasonable expectation of success including alanine 163 in the soluble HM1.24 antigen protein of Ichikawa et al. because the resulting protein lacking 17 rather than 18 amino acids would be reasonably expected to have the same properties.

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In addition, one of ordinary skill in the art would have had a reasonable expectation of success in using the modified soluble HM1.24 antigen protein of Ichikawa et al. to detect anti-HM1.24 antibodies according to the antibody-capture assay format of Harlow & Lane based on the teachings of Gastinel et al. that soluble receptors maintained the ability to bind to antibodies. Similarly, Lauffer et al. taught that soluble fusion protein of transmembrane receptors retain their biological activity.

Finally, with respect to the limitation that the test sample includes human body fluids, culture supernatants of cells or animal secretion, as discussed in detail above Harlow & Lane teach screening hybridoma supernatants in order to identify antibodies that bind an antigen of interest. As such, it would have been obvious to perform the above methods on hybridoma cell supernatants as part of the process of making and isolating anti-HM1.24 antibodies.

Alternatively (as discussed with respect to claim 18 below), because Harlow & Lane teach that antibodies circulate throughout the blood, it would have been further obvious to detect anti-HM1.24 antibodies in blood since this is where antibodies would normally be found.

It is also possible to analyze the teachings of Ichikawa et al. in view of those of Harlow & Lane, Gastinel et al., Lauffer et al., Laping et al., Lo et al., Matsukawa et al., and Browning et al. In particular, although Ichikawa et al. do not specifically direct the skilled artisan to employ the soluble HM1.24 antigen protein for the purpose of detecting anti-HM1.24 antibodies, known uses for antigens included using solid-phased antigen for the purpose of detecting cognate antibodies in immunochemical assays, as taught by Harlow & Lane.

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Further, it was known to use soluble forms of transmembrane receptors in place of full-length membrane-bound forms for technical reasons, as taught by Gastinel et al., Lauffer et al., Laping et al., and Lo et al. It was known to produce such soluble forms either by removal of the transmembrane domain (as taught by Gastinel et al. and Browning et al.) or alternatively via Fc fusions was known (as taught by Browning et al., Ishikawa et al., Lauffer et al., Laping et al., and Lo et al.). When choosing the latter course, it was further known to be desirable in some instances to subsequently remove the Fc tag (as taught by Laping et al., Matsukawa et al., and Lo et al.). Finally, although the soluble HM1.24 antigen protein of Ichikawa et al. lacks 18 rather than 17 amino acids from the C-terminus of SEQ ID NO:20, based on the knowledge of the amino acid sequence of HM1.24 as taught by Ichikawa et al. as well as the general knowledge in the art, one would reasonably expect the two proteins to possess the same properties.

With respect to claim 2, Harlow & Lane teaches binding antigens to a solid phase as discussed above. One would have had a reasonable expectation of success in binding the soluble HM1.24 antigen protein to a solid phase because Gastinel et al. taught that soluble receptors could be attached to any compatible, functional surface (column 10, lines 42-47; column 11, lines 62-67).

With respect to claim 6, Harlow & Lane teaches immobilization of antigens for the antibody-capture assay on microtiter plates (page 563, second paragraph).

With respect to claim 7, Harlow & Lane teaches using a secondary labeled reagent that will specifically recognize the antibody (i.e., a primary antibody against the antibody). See page 563, first paragraph and page 564. Therefore, when conducting antibody capture assays using soluble HM1.24 antigen protein to detect anti-HM1.24 antibodies as discussed above, it would

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have been further obvious to employ a labeled reagent that specifically recognized anti-HM1.24 antibodies in order to detect antigen-antibody binding.

With respect to claim 13, Harlow & Lane discuss how all immunoassays rely on labeled reagents for detection (pages 591-592). Suitable labels include radioactive compounds, enzymes, biotin, or fluorochromes (page 591, first paragraph).

With respect to claims 18-19, Harlow & Lane teach that antibodies circulate through the blood and lymph (see page 7). The teachings of Ishikawa et al. relate to human HM1.24. Therefore, when detecting HM1.24 antibodies according to the prior art methods as discussed above, it would have been further obvious to detect the antibodies in human fluids such as blood, as one of ordinary skill in the art would expect to find antibodies in these fluids.

4. Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane in view of Ishikawa et al., Gastinel et al., Lauffer et al., Laping et al., Lo et al., Matsuzawa et al., and Browning et al. as applied to claim 1 above, and further in view of Frank et al. (U.S. 5,646,115).

The references are as discussed in detail above. Harlow & Lane teaches antibody-capture immunochemical assays in which binding of antibody in a test sample to solid phase antigen is detected using an antibody specific to the test antibody. However, the references fail to specifically teach using a second antibody in addition to the antibody specific to the test antibody.

Frank et al. teach immunochemical assays in which antigen (saliva proteins) are immobilized on a solid phase and used to capture antibodies in a body fluid test sample (column

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34, line 22 to column 35, line 45). The reference teaches that the amount of antibody bound to the solid phase can be determined using one or more layers of secondary antibodies. For example, an untagged secondary antibody can be bound to a serum antibody (in the test sample) and the untagged secondary antibody can then be bound by a tagged tertiary antibody). See column 35, lines 35-45.

Therefore, it would have been further obvious to one of ordinary skill in the art to employ a second antibody (tagged tertiary antibody) as taught Frank et al. in addition to the primary antibody taught by Harlow & Lane in the method of Harlow & Lane, Ishikawa et al., Gastinel et al., Lauffer et al., Laping et al., Lo et al., Matsuzawa et al., and Browning et al. in order to achieve the same purpose, namely that of determining the amount of antibody in the test sample that is bound to the solid phase. More particularly, one would be motivated to include an additional antibody layer in this manner in order to determine the amount of anti-HM1.24 antibody in a test sample.

### **Response to Arguments**

5. With respect to the rejections of claims 1-2, 6-7, 13, and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane in view of Ishikawa et al., Gastinel et al., Lauffer et al., Laping et al., Lo et al., Matsuzawa et al., and Browning et al., Applicant's arguments filed 3/28/2011 have been fully considered but are not found persuasive.

6. Applicant argues that Ishikawa used an Fc-HM1.24 fusion protein, and does not disclose or suggest anything which would motivate a skilled person to remove the Fc portion from the fusion protein (reply, page 7, first paragraph).

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This is not found persuasive for the following reasons.

First, removal of the Fc portion from the Ishikawa Fc-HM1.24 fusion protein is not the only way that one of ordinary skill in the art could have arrived at the claimed invention. As such, patentability does not rest on whether one would be motivated to subsequently remove the Fc portion from the Ishikawa Fc-HM1.24 fusion protein.

See the Advisory action mailed 6/29/2010, and the Office action mailed 10/27/2010 at pages 18-20, item 10.

Second, Applicant's arguments that Ishikawa does not disclose or suggest anything which would motivate a skilled person to remove the Fc portion from the fusion protein are not persuasive as they amount to a piecemeal analysis of the references. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the Lapin et al. and Matsuzawa references provide motivation to remove Fc sequences. In addition, the Lo et al. reference also indicates that removal of the Fc domain from a fusion protein using a proteolytic cleavage site was well known in the prior art.

Applicant also makes reference to the Zettlmeissl et al. ("Seed") reference, as disclosing that Fc fusions were known to be advantageous in terms of serum survival. Applicant apparently argues that one would not be motivated to remove the Fc portion from the Fc fusion protein of Ishikawa et al. because one would lose this advantage of prolonged half life. See Reply, page 7, first paragraph and also at pages 9-10.

This argument has been previously advanced and is not persuasive for reasons of record (Office action mailed 20/27/2010 at pages 19-21). While serum half-life might be of tantamount interest when preparing reagents for in vivo administration of drugs, Applicant has not established why this goal would be critical in the case of an in vitro immunoassay method. These are wholly distinct methods that occur on very different time scales. No credible evidence has been advanced to show that one would be deterred from removing an Fc portion out of concern that the resulting protein would have an unacceptable half-life in an immunoassay due to brief contact with a serum sample. Likewise, Applicants have not shown that one would be concerned about serum half-life when performing in vitro immunoassay methods that do not even use serum, as are also encompassed by the claims.

Applicant further argues that stability is also important for in vitro experiments, arguing as above that one would not be motivated to remove the Fc portion from the fusion protein of Ishikawa et al. since such Fc domains were known to prolong serum half-life. See Reply, pages 9-10. Applicant points to the Zettlmeissl et al. ("Seed") reference at Figure 4 and at pages 350-351. However, none of the passages indicated teach that Fc portions must not be removed when using fusion proteins for in vitro immunoassays. Rather, the Seed reference discusses the in vivo serum stability of a wholly distinct protein, CD4. As such, the applicability of the Seed reference to in vitro methods such as those claimed, and in particular those involving in vitro immunoassays using HM1.24, is not apparent.

Counsel again suggests that proteolysis was a known problem for ELISA assays (Reply, page 9) but still has not advanced any evidence of this asserted problem.

At the time of the invention, ELISA assays were routinely performed using fragments of antibodies lacking the Fc portions as capture reagents, as evidenced for example by Matsuzawa. As such, the evidence of record fails to support Applicant's position that proteolysis of protein reagents being used in ELISA was a significant and well-documented problem in the art such that the ordinary artisan would have been led away from removing the Fc portion of the Ishikawa fusion protein.

5. Applicant further argues that Gastinel discloses a soluble Fc receptor that was created by removing a transmembrane domain, and that the secreted Fc receptor was purified using an antibody affinity column (Reply, page 7, second and third paragraphs).

The import of these remarks is not clear. The teachings of Gastinel noted by Applicant rather appear to support a determination of obviousness, as they indicate that receptors in which the transmembrane domain has been removed nonetheless retain the ability to bind to antibodies.

7. Applicant argues that none of the cited documents show that the truncated form of HM1.24 has the correct conformation and can still be recognized by the HM1.24 antibody. Applicant argues that Ishikawa et al. only discloses HM1.24 fusion proteins of the soluble protein with an Fc portion. See Reply, page 7.

This is not found persuasive because initially, the claims do not require the HM1.24 antigen protein to be in any particular conformation.

Furthermore, Applicant makes reference to the ability of the truncated form of HM1.24 to be recognized by "the" HM1.24 antibody (see also page 10). However, the claims do not require assaying for any particular HM1.24 antibody. As such, there is no requirement that one must

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select an HM1.24 antigen that binds to "the" antibody. Proteins present multiple epitopes available for antibody binding.

In addition, Applicant has not established establish that one of ordinary skill in the art would have doubted that a truncated HM1.24 protein would be in an incorrect conformation or would exhibit a loss of antibody binding. The general arguments of counsel do not establish that one of ordinary skill in the art would lack a reasonable expectation of success in producing a soluble HM1.24 antigen lacking the transmembrane domain. There is insufficient evidence of record to support that such problems would have been expected and as such, Applicant has not established why the ordinary artisan would lack a reasonable expectation of success in combining the reference teachings as claimed.

Notwithstanding this, Applicant's arguments that none of the references show that the truncated form of HM1.24 can still be recognized by the HM1.24 antibody are not found persuasive for the following reasons. Applicant's Reply elsewhere points to the Goto et al. reference (Blood Vol. 84, No. 6 (1994) 1922-1930) and argues that this reference teaches a cell-based ELISA for anti-HM1.24 antibody (see Reply, page 9, last full paragraph). Indeed, in Goto et al. the HM1.24 antigen was expressed on B cells and used to bind to the antibody (see especially the abstract and page 1922). As also acknowledged by Applicant, the HM1.24 antigen was known in the prior art to be a transmembrane protein (this is taught for example by both Goto et al. and Ishikawa et al.). The Goto et al. reference indicates that HM1.24 antigen expressed on cells is capable of binding to the HM1.24 antibody. The ordinary artisan would therefore appreciate that the antibody binds to extracellular portions of the HM1.24 antigen, and not to the transmembrane or intracellular domains. Were this not the case, the antibody would be

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unable to bind to HM1.24 on cells since the transmembrane domain would be embedded in the cell membrane and therefore unavailable for antibody binding. Similarly, the intracellular domain would be inside the cell and unavailable for antibody binding.

The evidence of record therefore indicates that known anti-HM1.24 antibodies bound to the extracellular portion of the antigen. As such, Applicant's arguments to the effect that removal of the transmembrane domain of the antigen might have been predicted to ablate antibody binding are not persuasive, since the truncated antigen would still contain the portions of the antigen necessary for antibody binding.

6. Applicant further argues that Matsuzawa teaches avoiding any Fc portion in an immunoassay for the detection of a soluble protein and also uses antibody fragments without the Fc portion. Applicant argues that the anti-HM1.24 antibody comprises an Fc portion. Applicant reasons that consequently, one skilled in the art reading Matsuzawa would be motivated to either remove the Fc portion from both the antibody and the antigen, or from neither of them (Reply, pages 7-8).

Initially, Applicant's arguments that "the anti-HM1.24 antibody comprises an Fc portion" are not persuasive because as above, the claims do not require detection of any particular anti-HM1.24 antibody. The antibody being detected could be a whole antibody or a Fab fragment, for example. As such, even if Applicant's arguments are adopted that one would be motivated based on Matsuzawa to also remove the Fc portion from the antibody being detected, this would still read on the claimed invention.

However, a reading of Matsuzawa does not support Applicant's characterization of the reference as teaching that one would be motivated to either remove the Fc portion from both the

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antibody and the antigen, or from neither of them. It is true that Matsuzawa detected an antigen using an antibody as the immunoassay reagent, while the instant claims detect an antibody using an antigen as the immunoassay reagent. However, Matsuzawa clearly teaches that Fc fragments present on an immunoassay reagent used to bind components in the sample may interfere with components in the sample such as rheumatoid factor. As such, the ordinary artisan would have recognized that Fc fragments present on either an antibody or an antigen immunoassay reagent could cause interference. There is nothing in the reference, however, that would direct one to remove Fc fragments from the analyte in the sample that is being detected in the immunoassay. Since the purpose of the immunoassay is to detect an analyte in a complex mixture, it would be nonsensical to first isolate the analyte, remove a portion thereof, and then re-introduce it into the sample for detection. For these reasons, Applicant's arguments that Matsuzawa teaches avoiding any Fc portion on any component in an immunoassay (i.e., in either the immunoassay reagent or the analyte to be measured) cannot be adopted.

7. With respect to Laping et al., Applicant argues that the reference specifically points out that the Fc portion has its advantages and should therefore only be removed when it is a hindrance. Applicant argues that such a hindrance was not known for the HM1.24 protein. See Reply, page 8, last paragraph.

This is not found persuasive because as discussed, above, Laping et al. teach removal of the Fc portion in cases in which the fusion protein is to be used as an antigen. As the immunoassay methods taught by the prior art combination involve using the HM1.24 protein as an antigen for binding to antibodies, one would be motivated to remove the Fc portion based on

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this teaching by Laping et al. because the protein is being used as an antigen. An express suggestion to remove the Fc portion in the case of the HM1.24 protein is not required.

8. Applicant further argues that although it was known that HM1.24 is a transmembrane protein, the claimed method [involving truncated HM1.24] was not used in prior art methods of detecting the anti-HM1.24 antibody. Applicant urges that this is evidence that the claimed method was not obvious. See Reply, page 9, last full paragraph.

This is not found persuasive because it does not necessarily follow that an invention that has not yet been experimentally performed is non-obvious.

9. Applicant also makes references to the ability of the soluble HM1.24 antigen to form a dimer (Reply, page 10). This argument has been previously advanced and is not found persuasive for reasons of record (Advisory action mailed 6/29/2010). There is nothing in the claims that recite or require that the antigen be dimeric.

10. Applicant further remarks on the increased sensitivity of the assay, and on detecting the anti-HM1.24 antibody at low concentrations (Reply, page 10). Such arguments by counsel fail to constitute sufficient evidence of unexpected results.

### Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO**

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MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/  
Examiner, Art Unit 1641

/GAILENE R. GABEL/  
Primary Examiner, Art Unit 1641

4/6/11